CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761432Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 15, 2025
To:	Nina Mani Regulatory Project Manager **Division of Antivirals (DAV)**
Through:	Barbara Fuller, MSN, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Wendy Lubarsky, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	ENFLONSIA (clesrovimab-cfor)
Dosage Form and Route:	injection, for intramuscular use
Application Type/Number:	BLA 761432
Applicant:	Merck Sharp & Dohme LLC

1 INTRODUCTION

On October 10, 2024, Merck Sharp & Dohme LLC submitted for the Agency's review Biologics License Application (BLA) 761432 for ENFLONSIA (clesrovimab-cfor). The proposed indication for this BLA is prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antivirals (DAV) on November 8, 2024, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ENFLONSIA (clesrovimab-cfor) injection, for intramuscular use.

2 MATERIAL REVIEWED

- Draft ENFLONSIA (clesrovimab-cfor) PPI received on October 10, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 5, 2025.
- Draft ENFLONSIA (clesrovimab-cfor) Prescribing Information (PI) received on October 10, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 5, 2025.
- Approved BEYFORTUS (nirsevimab-alip) comparator labeling dated August 22, 2024.
- Approved SYNAGIS (palivizumab) comparator labeling dated May 12, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

MARIA T NGUYEN
05/15/2025 06:18:11 PM
DMPP-OPDP review of clesrovimab-cfor (ENFLONSIA) BLA 761432 PPI

WENDY R LUBARSKY
05/16/2025 09:27:00 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 16, 2025

To: Nina Mani, Regulatory Project Manager
Division of Antivirals (DAV)

From: Wendy Lubarsky, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for ENFLONSIA (clesrovimab-cfor) injection, for intramuscular use

BLA: 761432

Background:

In response to DAV's consult request dated November 8, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original BLA submission for Enflonsia.

PI/PPI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on May 2, 2025, and we do not have any comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI, and comments were sent under separate cover on May 16, 2025.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on May 16, 2025, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Wendy Lubarsky at (240) 402-7721 or wendy.lubarsky@fda.hhs.gov .

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/s/

WENDY R LUBARSKY
05/16/2025 11:27:16 AM

USE-RELATED RISK ANALYSIS AND COMPARATIVE ANALYSES REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 6, 2025
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	BLA 761432
Product Name, Dosage Form and Strength:	Enflonsia[a] (clesrovimab-xxxx)[b] Injection, 105 mg/0.7 mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Rx
Device Constituent:	Prefilled Syringe (PFS)
Applicant/Sponsor Name:	Merck Sharp & Dohme LLC (Merck)
Submission Date:	October 10, 2024, October 16, 2024, November 25, 2024
OSE TTT #:	2024-11256
DMEPA 1 Safety Evaluator:	Keith Christopher, PhD
DMEPA 1 Team Leader:	Matthew Barlow, RN, BSN
DMEPA 1 Associate Director for Human Factors:	Ariane O. Conrad, PharmD, BCACP, CDCES, FISMP

[a] The proprietary name, Enflonsia, for this proposed product was conditionally approved on March 7, 2025; however, MK-1654 was used throughout the submission as a placeholder for this proposed product. Therefore, the proprietary name placeholder, MK-1654, is used throughout the review.
[b] The non-proprietary name suffix for this product has not yet been determined. Therefore, the placeholder "clesrovimab-xxxx" is used to refer to the non-proprietary name for this product and is not intended to be included in the final labels and labeling.

1 REASON FOR REVIEW

The review evaluates the use-related risk analysis (URRA) and Human Factors summary report submitted under BLA 761432 for Enflonsia (clesrovimab-xxxx) Prefilled Syringe (PFS) to determine whether Merck Sharp & Dohme LLC (Merck) needs to submit human factors (HF) validation study results to support their marketing application.

1.1 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review	
Material Reviewed	Section/Appendix
Product Information	Section 1.2
Background Information Previous HF Reviews (DMEPA)	Section 1.3
Use-Related Risk Analysis and HF Related Supporting Documents	Appendix A
Information Requests Issued During the Review	Appendix B
Product Samples, Labels, and Labeling	Appendix C

N/A=not applicable for this review

1.2 PRODUCT DESCRIPTION

Table 2. Relevant Product Information for MK-1654	
Product Name	Enflonsia
Application Number	BLA 761432
Initial Approval Date	N/A
Active Ingredient	clesrovimab-xxxx
Indication	To prevent respiratory syncytial virus (RSV) in infants (b) (4)
Route of Administration	Intramuscular injection
Dosage Form	Injection
Strength	105 mg/0.7 mL
Dose and Frequency	<u>Neonates and Infants: First RSV Season</u> The recommended dose is 105 mg administered as a single intramuscular (IM) injection. For neonates and infants born during the RSV season, administer starting from birth. For infants born outside the RSV season, administer once

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for MK-1654</th></tr>
<tr><td></td><td>prior to the start of their first RSV season considering (b) (4) duration of protection.

<u>Infants Undergoing Cardiac Surgery with Cardiopulmonary Bypass</u>
For infants undergoing cardiac surgery with cardiopulmonary bypass during the RSV season, an additional 105 mg dose is recommended as soon as the infant is stable after surgery to ensure adequate clesrovimab-xxxx serum levels.</td></tr>
<tr><td>How Supplied</td><td>MK-1654 injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution supplied as follows:

Carton containing one or ten single-dose prefilled type I glass syringe(s) with Luer Lock and plunger stopper. The prefilled syringe is not made with natural rubber latex.

<table>
<tr><th>Prefilled syringe</th><th>Pack Size</th><th>NDC</th></tr>
<tr><td>105 mg/0.7 mL single-dose</td><td>Carton of 1</td><td>0006-5073-01</td></tr>
<tr><td>105 mg/0.7 mL single-dose</td><td>Carton of 10</td><td>0006-5073-02</td></tr>
</table>
(b) (4)</td></tr>
<tr><td>Storage</td><td>Store in a refrigerator between 36°F to 46°F (2°C to 8°C)</td></tr>
<tr><td>Container Closure/Device Constituent</td><td>(b) (4)</td></tr>
<tr><td>Intended Users</td><td>Healthcare professionals (HCPs)</td></tr>
</table>

Table 2. Relevant Product Information for MK-1654	
Intended Use Environment(s)	Healthcare Environments

1.3 RELEVANT REGULATORY HISTORY RELATED TO ENFLONSIA'S HUMAN FACTORS DEVELOPMENT PROGRAM

On January 6, 2025, we searched for previous DMEPA reviews and FDA/Merck interactions relevant to this current review using the terms, "MK-1654" and "clesrovimab". See details below.

- [redacted] Merck submitted a URRA, HF summary report, and a justification for not submitting HF validation study results for the proposed [redacted] under IND 130097. We determined Merck does not need to submit HF validation study data with their future marketing application for the proposed MK-1654 PFS, to be used by healthcare professionals (HCPs).[c]
- On October 10, 2024, Merck submitted their marketing application (BLA 761432), which included their URRA, HF summary report, and justification for not submitting HF validation study results, which are the subjects of this review

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide our evaluation of the URRA.

2.1 USE-RELATED RISK ANALYSIS

Merck submitted BLA 761432 for their proposed product, MK-1654 PFS, which included a URRA and HF summary report document containing aside-by-side comparison between [redacted] and the currently proposed version of the PFS and user interface. Additionally, Merck provided a list of changes to the user interface for consideration of changes to the user interface:

- Change of color to plunger rod [redacted]
- Carton/PFS holder is paperboard [redacted]
    - Tray is now built into the carton and not removable. The tray is designed to have users grab the body of the PFS and not the ends.
- Change in plunger stopper supplier
    - There are no changes in the size/dimensions.
- Viscosity of solution has decreased ([redacted] to 8.5 cP at room temperature)

[c] Lee, S H. URRA Review for clesrovimab (IND 130097). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 NOV 09. TTT # 2021-1464

    - We reached out to our colleagues in the Office of Pharmaceutical Quality (OPQ) to gain input regarding the acceptability of the change in viscosity. OPQ confirmed they have no concerns with the change. As such, we find the change in viscosity acceptable.

- Break loose force and extrusion force
    - Former break loose force increased from (b) (4) N to 5 N and the extrusion force decreased from (b) (4) N to 9 N. We reached out to our colleagues in OPQ for their input regarding this change, and they confirmed that the changes in force were within the acceptable ranges. As such, we find the changes acceptable.
- Dosing change for high-risk infants (will be given a second injection)
    - The administration of a second injection is not a new or unique task for products administered by HCPs in a clinical setting. Therefore, we find the residual risk associated with this dose change to be acceptable.

However, it was not clear what changes were made to the URRA. Therefore, on November 21, 2024, we issued an information request to Merck requesting that they submit their revised URRA in tracked changes. On November 25, 2024, Merck responded with a revised URRA in tracked changes and we confirmed that there were no changes in the URRA.

Based on our independent expert review along with input from our OPQ colleagues, we have determined that the aforementioned changes to the user interface do not impact the risk control measures, did not change critical task categorization, and are not new, differing, or unique risks associated with the proposed product. As such, we maintain our determination that Merck Sharpe & Dohme LLC does not need to submit HF validation study results to support their marketing application.

3 CONCLUSION

Our review of the URRA did not identify any new, differing, or unique risks for the proposed Enflonsia PFS. As such, we maintain our determination that Merck Sharpe & Dohme LLC does not need to submit HF validation study results to support their marketing application. We provide our response in Section 3.1.

3.1 RECOMMENDATIONS TO MERCK SHARP & DOHME LLC

Based on our review Human Factors (HF) Summary Report and Use-related Risk Analysis (URRA) and justification, we have determined that you do not need to submit HF validation study data with your marketing application for the MK-1654 prefilled syringe (PFS) for administration by healthcare professionals. We have no HF recommendations for this marketing application.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. USE-RELATED RISK ANALYSIS AND HF RELATED SUPPORTING DOCUMENTS

The use-related risk analysis (URRA) for Enflonsia submitted on October 10, 2024 can be accessible in EDR via: \\CDSESUB1\EVSPROD\bla761432\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\rsvmabproph1\5354-other-stud-rep\06dy9l\06dy9l.pdf

APPENDIX B. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On 10/11/2024, we issued an Information Request (IR) to request their PFS samples for review. On 10/16/2024, Merck did provide a response that can be accessed in EDR via: \\CDSESUB1\EVSPROD\bla761432\0004\m1\us\quality-information-amendment-16oct2024.pdf

On 11/21/2024, we issued an Information Request (IR) to request for an updated URRA with tracked changes in comparison to previously reviewed URRA in IND 130097. On 11/25/2024, Merck did provided a response that can be accessed in EDR via: \\CDSESUB1\EVSPROD\bla761432\0011\m5\53-clin-stud-rep\535-rep-effic-safety-stud\rsvmabproph1\5354-other-stud-rep\08mqzm\08qgz7-tracked.pdf

APPENDIX C. PRODUCT SAMPLES, LABELS, AND LABELING

C.1 Product Samples

The product samples were not submitted for our review.

C.2 Labels and Labeling Images

Carton Labeling:

(b) (4)

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/s/

KEITH G CHRISTOPHER
05/06/2025 09:13:27 AM

MATTHEW J BARLOW
05/06/2025 09:15:51 AM

ARIANE O CONRAD
05/06/2025 10:31:48 AM

Clinical Inspection Summary

Date	05 May 2025
From	Elena Boley, MD, MBA Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Nina Mani, PhD, MPH, Senior Regulatory Project Manager Yugenia Hong-Nguyen, MD, Clinical Reviewer Aimee Hodowanec, MD, Clinical Team Leader Division of Antivirals
NDA #	BLA 761432
Applicant	Merck Sharp & Dohme LLC
Drug	Clesrovimab
NME	Yes
Proposed Indication	The prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season
Consultation	10 Oct 2024
Summary Goal	05 May 2025
Action Goal Date	10 Jun 2025
PDUFA Date	10 Jun 2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Baker, Zar, Franckling-Smith, Etchegaray, and Novoa Pizarro, as well as the sponsor – Merck Sharp & Dohme, LLC – were inspected in support of BLA 761432. The clinical investigator inspections covered Protocols MK-1654-004 (Drs. Baker, Zar, Etchegaray, and Novoa Pizarro) and MK-1654-007 (Dr. Franckling-Smith), and the sponsor inspection covered both protocols. The clinical investigator (CI) inspections have the following findings:

1. Underreporting of Adverse Events (AEs)

For Protocol MK-1654-004, two AEs (vomiting and not eating well) at the site of Dr. Baker and three AEs (nasal mucus/sneezing, mild colic, and defecation problem) at the site of Dr. Novoa Pizarro were not reported to the FDA. For Protocol MK-1654-007, one AE (increasing ringworm) at the site of Dr. Franckling-Smith was not reported. The proposed label submitted by the sponsor appears not to include these AEs. We recommend the review division consider these underreported AEs.

2. Underreporting of Respiratory Syncytial Virus (RSV)-associated Medically Attended Lower Respiratory Infection (MALRI)

At the site of Dr. Etchegaray, source documents showed that subject (b) (6) (in the placebo group) had RSV-positive RT-PCR test results on Day 56 with cough and wheezing, therefore

meeting criteria for RSV-associated MALRI. This case was not reported in the data line listings submitted by the sponsor. Because subject (b) (6) was randomized to the placebo group, the failure to report this case should favor placebo over clesrovimab.

Otherwise, the inspections found that the primary efficacy and safety data for Study MK-1654-004 and the safety issues of interest to the review division for Study MK-1654-007 were verifiable. Overall, the inspections indicate that these studies appear to have been conducted adequately, and the data generated by these inspected CI sites and reported by the sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

BLA 761432 was submitted on October 10, 2024, to support the efficacy and safety of clesrovimab for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season. The two clinical studies supporting the application were the following:

Protocol MK-1654-004

- ***Title:*** "A Phase 2b/3 Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-1654 in Healthy Pre-Term and Full-Term Infants"

This was a Phase 2/3, randomized, double-blind, placebo-controlled, multicenter trial in healthy preterm and full-term infants. The primary objective was to evaluate the efficacy of MK-1654 (clesrovimab) compared to placebo as assessed by the incidence of RSV-associated medically attended lower respiratory infection (MALRI, outpatient and inpatient) from Day 1 through Day 150 postdose.

Eligible participants were healthy male and female early and moderate pre-term infants (≥29 to <35 weeks gestational age) and late pre-term and full-term infants (≥35 weeks gestational age) up to 1 year of age who were entering their first RSV season at the time that written informed consent was collected from the infant's legally authorized representative (LAR).

Patients were excluded if – per local guidelines or professional society recommendations – it was recommended that they receive palivizumab; if they had a recent illness with rectal temperature ≥100.5°F (≥38.1°C) or axillary temperature ≥100.0°F (≥37.8°C) within 72 hours predose; or if they had received any vaccine or mAb for the prevention of RSV (including receipt of maternal RSV vaccination during the mother's pregnancy). See protocol for full exclusion criteria.

The study consisted of a 1-day screening, randomization, and intervention period and a follow-up period that concluded 365 days postdose. After screening, participants were randomized in a 2:1 ratio to receive a single dose of clesrovimab or placebo. Randomization was stratified by region (northern hemisphere vs southern hemisphere), gestational age (early and moderate pre-term infants [≥29 to <35 weeks gestational age] vs late pre-term and full-term infants [≥35

weeks gestational age]), and chronological age at the time of consent (<6 months of age vs ≥6 months of age).

After randomization, on Day 1, all participants were to receive the assigned study intervention (clesrovimab or placebo administered via IM injection) and were observed for 30 minutes postdose. Participants were to be followed for at least 365 days after receiving study intervention. Efficacy surveillance for respiratory infection symptoms were to be conducted for 180 days postdose. Adverse events (AEs) were to be collected for 42 days postdose, and serious adverse events (SAEs) were to be collected for the duration of study participation. A subset of participants (the first 1650 participants enrolled) continued to be followed throughout the second RSV season, from Day 365 through Day 515 postdose.

Active surveillance for respiratory infection symptoms was performed throughout the study. LARs were instructed to call the site if a participants had respiratory infections symptoms. Additionally, surveillance for respiratory infection symptoms was performed by site staff via weekly phone calls. If respiratory infection symptoms were reported or worsened when a participant was seen in an outpatient or inpatient clinical setting and respiratory signs or symptoms were confirmed or observed, a nasopharyngeal (NP) swab was collected to determine RSV association.

Additionally, each participant's LAR was provided an electronic "diary card" and instructed by the investigator or staff on its use and how to identify suspected adverse events of special interests (AESIs) such as anaphylaxis/hypersensitivity events and rash events. The electronic diary card was reviewed during weekly surveillance phone calls and at several additional telephone calls before it was collected at Visit 3 (i.e., at the end of the 42-day period). Retraining by the site was provided as soon as possible if any noncompliance with the electronic diary card was identified.

Important efficacy endpoints include the following:

Primary efficacy endpoint: RSV-associated MALRI (outpatient and inpatient), defined as the following seen in an outpatient or inpatient clinical setting:

- Cough or difficulty breathing; AND
- 1 or more of the following: wheezing, chest wall in-drawing/retractions, rales/crackles, hypoxemia, tachypnea, dehydration due to respiratory symptoms; AND
- RSV-positive RT-PCR NP sample

Protocol MK-1654-007

- ***Title****:* "A Phase 3, Multicenter, Randomized, Partially Blinded, Palivizumab-Controlled Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of MK-1654 in Infants and Children at Increased Risk for Severe RSV Disease"

This was a Phase 3, randomized, partially-blinded, active-controlled, multicenter trial in infants and children at increased risk for severe RSV disease. The primary objective was to evaluate

the safety and tolerability of clesrovimab compared to palivizumab in their first RSV season as assessed by the proportion of participants experiencing AEs.

Eligible participants were male and female infants ≤35 weeks gestational age or infants with chronic lung disease (CLD) of prematurity or hemodynamically significant chronic heart disease (CHD) who had a chronological age from birth up to 1 year and were entering their first RSV season at the time of consent.

Patients were excluded if they required mechanical ventilation at time of enrollment, had a life expectancy <6 months, had known hepatic or renal dysfunction or a chronic seizure disorder, were hospitalized at the time of randomization unless discharge was expected within 7 days after randomization, or had severe immunodeficiency or were severely immunocompromised. They were also excluded if they had a recent illness with rectal temperature ≥100.5°F (≥38.1°C) or axillary temperature ≥100.0°F (≥37.8°C) within 72 hours predose; or if they had received any vaccine or mAb for the prevention of RSV, including receipt of maternal RSV vaccination during the mother's pregnancy. See protocol for full exclusion criteria, including exclusion criteria for participation in RSV season 2.

Each participant was screened, enrolled to participate in either 1 or 2 RSV seasons, and randomized in a 1:1 ratio (stratified by region [northern vs southern hemisphere] and participant condition [CLD, CHD, <29 weeks gestational age without CLD or CHD, or ≥29 weeks gestational age without CLD or CHD]) to one of two groups:

- Clesrovimab (experimental) group:
  - RSV season 1: clesrovimab, single dose at Day 1 visit and placebo at Day 28 visit
  - RSV season 2: clesrovimab, single dose at Day 1 visit for RSV season 2
- Palivizumab (active comparator) group:
  - RSV season 1: palivizumab, 3 to 5 monthly doses starting at the Day 1 visit
  - RSV season 2: clesrovimab, single dose at Day 1 visit for RSV season 2

On RSV Season 1 Day 1, all participants enrolled were administered study treatment doses as scheduled and were followed for 365 days. Participants enrolled for 2 RSV seasons also received a dose of clesrovimab in RSV Season 2 and were followed for an additional 180 days postdose. Most participants remained in the study for 365 days (1 RSV season) from the time the participant's LAR provided documented informed consent through the final contact. Participants who enrolled, consented, and remained eligible for 2 RSV seasons participated in the study for up to 575 days from the time the participant's LAR provided documented informed consent through the final contact.

The study consisted of 2 parts: Part 1 of the study was to be double-blind, and Part 2 was to be open-label. After consent was obtained from the LAR, Part 1 began with a 1-day period that included screening, randomization, and administration of the first dose of the study treatment for RSV Season 1. After study treatment administration, each participant then entered a follow-up period for RSV Season 1 (postdose day 1 through day 60), during which participants received a second dose on day 28 (the clesrovimab group received placebo and the palivizumab group received their second dose of their 3-5 monthly dose regimen). At the Day

60 visit, all participants were unblinded and underwent follow-up for the remainder of their participation in the study (through RSV Season 1 +/- RSV Season 2).

For participants initially enrolled and consented to participate in RSV Seasons 1 and 2, inclusion/exclusion criteria were rechecked at the Day 240 visit, and those who remained eligible continued in the study through the RSV Season 2. All RSV Season 2 participants received a single dose of clesrovimab and were followed up through Day 180 post season 2 dosing (for a total of 575 days from the time the LAR provided informed consent). During the follow up periods for RSV season 1 and 2, participants received telephone calls and completed several study visits during which physical examinations were completed, medications and AEs (including e-diary data) were reviewed, efficacy surveillance was performed to monitor the incidence of RSV-associated MALRI and hospitalization, and blood samples were collected (as specified in the protocol).

If during the RSV season a participant underwent 1) ECMO or 2) surgical intervention for CHD and required cardiopulmonary bypass during the procedure, the site was to consult the sponsor regarding any additional post-surgery dose of clesrovimab or palivizumab at the recommended dose based on their randomization allocation and the RSV season at the time of the procedure.

Similar to Protocol MK-1654-004, each participant's LAR received an electronic diary and instructions on its use and how to identify suspected AESIs such as anaphylaxis/ hypersensitivity events and rash events. The LAR recorded complaints, illnesses, and temperature data from Day 1 through Day 42 post Dose 1 and through Day 14 after each subsequent dose. The electronic diary was reviewed at several times before it was collected, and retraining by the site was to be provided if participants were noted to be noncompliant with its use. Sites reviewed with the LAR all complaints or illnesses to determine if they met AE criteria.

Important safety endpoints include the following:

Primary safety endpoints of interest to the review division: Adverse events, including:

- Solicited injection-site AEs from Days 1 through 5 after each dose.
- Solicited daily body temperature, with fever defined as rectal temperature ≥102.2°F (≥39.0°C) or axillary temperature ≥101.7°F (≥38.7°C) from Days 1 through 5 after each dose.
- Anaphylaxis/hypersensitivity AESIs from Days 1 through 42 post Dose 1.
- Rash AESIs from Days 1 through 42 post Dose 1.

Details relevant to Study MK-1654-004

Study MK-1654-004 was conducted at 217 centers in 24 countries (Argentina, Belgium, Canada, Chile, China, Colombia, Denmark, Finland, France, Israel, Italy, Japan, Malaysia, Mexico, Peru, Philippines, Poland, Romania, South Africa, South Korea, Thailand, Turkey, United Kingdom, and the United States). The first subject's visit occurred on April 7, 2021, and the last

subject's visit for the interim complete study report occurred on March 4, 2024. Of the 3632 subjects who were randomized (2421 subjects were in the clesrovimab group and 1211 subjects were in the placebo group), 3153 subjects (87%) completed the study. The original protocol was dated July 28, 2020. There were five protocol amendments, and the final amendment was dated December 2, 2022.

Details relevant to Study MK-1654-007

Study MK-1654-007 was conducted at 109 centers in 27 countries (Australia, Canada, Chile, Colombia, Czech Republic, Finland, France, Germany, Greece, Hong Kong, Hungary, Italy, Japan, Malaysia, Mexico, New Zealand, Norway, Peru, Puerto Rico, Singapore, South Africa, Spain, Taiwan, Thailand, Turkey, United Kingdom, and United States). The first subject signed their informed consent on November 30, 2021, and the last subject's visit for the interim complete study report occurred on February 5, 2024. Of the 901 subjects that were randomized (450 subjects received clesrovimab and 451 subjects received Palivizumab), 458 subjects (51%) completed the study. The original protocol was dated May 17, 2021. There were two protocol amendments, and the final amendment was dated May 18, 2022.

III. RESULTS (by site):

1. **Jeffrey B. Baker, MD**
   Site #75
   Protocol: MK-1654-004
   187 East 13th Street
   Idaho Falls, ID 83404
   PDUFA Inspection Dates: February 24-28, 2025

At this site for Protocol MK-1654-004, 42 subjects were screened (inclusive of one subject, (b) (6), who was transferred to Dr. Baker's site from another site), 40 subjects were randomized, 39 completed the study through the primary efficacy data collection time point (150 days), and 36 subjects completed the study at this site (day 515). The single subject who did not complete the study through Day 150, subject (b) (6) (in the clesrovimab group), was lost to follow up on day 92. The remaining 3 subjects discontinued after Day 150 were subject (b) (6) (in the clesrovimab group) who was lost to follow up, subject (b) (6) (in the clesrovimab group) who withdrew consent, and subject (b) (6) (in the placebo group) who withdrew for personal reasons.

The inspection evaluated the study records for the two subjects who were screen failures and 30 of the 40 randomized subjects for Protocol MK-1654-004. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; institutional review board (IRB) submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data; adverse event (AE) reporting; protocol deviations; drug accountability logs; monitor logs and sponsor reports; and other regulatory documentation.

During the inspection, for these 30 randomized subjects who completed the study through day 150, the primary efficacy endpoint data – clinical signs and symptoms (wheezing, chest wall in-drawing/retractions, rales/crackles, hypoxemia, tachypnea, or dehydration due to respiratory symptoms and cough/difficulty breathing) and nasopharyngeal (NP) sample RT-PCR results – were reviewed in paper and PDF format, respectively. These data were verified against the data line listings provided by the sponsor (for the clinical signs and symptoms) and those compiled by this reviewer using the line listings generator. No discrepancies were noted.

Adverse events were reviewed for these 30 randomized subjects. The inspection found that "vomiting" and "not eating well" – both of which were experienced by the subject (b) (6) before they were transferred to this site – were documented as adverse events in the eCRF but were not reported in the data line listings provided by the sponsor. There was no other evidence of underreporting of adverse events.

Reviewer's comment: The two unreported AEs of "vomiting" and "not eating well" experienced by subject (b) (6) (in the placebo group) were not included in the proposed label. The reporting of these two AEs experienced by subject (b) (6) was the sponsor's responsibility, as the clinical investigator entered these AEs properly in the eCRF. We refer these two unreported AEs to the review division for consideration.

2. **Heather Joy Zar, MBBCh, PhD**
   Site #2502
   Protocol: MK-1654-004
   MRC Unit on Child and Adolescent Health-
   Department of Paediatrics and Child Health
   Corner of Klipfontein and Milner Road Rondebosch
   Reach Unit B11
   Cape Town, Western Cape 7700
   South Africa
   PDUFA Inspection Dates: March 3-7, 2025

At this site for Protocol MK-1654-004, 149 subjects were screened, 146 subjects were randomized, 140 subjects completed the study through measurement of the primary efficacy endpoint (day 150), and 129 subjects completed the entire study (Day 515). Of the 146 randomized subjects, two subjects were discontinued at the investigator's discretion after randomization and were never dosed with study drug (subjects (b) (6), both in the placebo group). Of the 4 subjects who discontinued before the end of the timeframe during which the primary efficacy endpoint (Day 150) was measured, 2 died (subjects (b) (6) in the clesrovimab group died on Day 60 due to suspected sudden infant death syndrome and (b) (6) in the placebo group died on Day 134 due to unknown causes, both "non-cases"), one subject (subject (b) (6) in the clesrovimab group, a "non-case") was lost to follow up on Day 148, and one subject (subject (b) (6) in the clesrovimab group, a "case") was lost to follow up on Day 101.

The remaining subjects who discontinued did so after Day 150 (and before Day 515). Those included 8 subjects lost to follow up (subjects (b) (6), all in

the placebo group, and subjects (b) (6), all in the clesrovimab group), 2 subjects who died (subject (b) (4) in the placebo group died on study Day 271 and subject (b) (6) in the clesrovimab group died on study Day 260), and one subject (subject (b) (6) in the clesrovimab group) who terminated due to withdrawal of consent.

The inspection evaluated the study records for 36 of the randomized subjects for Protocol MK-1654-004. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; Independent Ethics Committee (IEC) submissions and approvals; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; monitor logs and sponsor reports; and other regulatory documentation. Informed consent documents were reviewed for 100% of randomized subjects.

During the inspection, for these 36 randomized subjects who completed the study through Day 150, the primary efficacy endpoint data – clinical signs and symptoms (wheezing, chest wall in-drawing/retractions, rales/crackles, hypoxemia, tachypnea, or dehydration due to respiratory symptoms and cough/difficulty breathing) and NP sample RT-PCR results – were reviewed in paper and PDF format, respectively. These data were verified against the data line listings provided by the sponsor. No discrepancies were noted.

Adverse events were reviewed for these 36 randomized subjects. There was no evidence of underreporting of AEs.

3. **Zoe Taryn Franckling-Smith, MBChB**
   Site # 710
   Protocol: MK-1654-007
   MRC Unit on Child and Adolescent Health-
   Department of Paediatrics and Child Health
   Corner of Klipfontein and Milner Road Rondebosch
   Reach Unit B11
   Cape Town, Western Cape 7700
   South Africa
   PDUFA Inspection Dates: March 3-7, 2025

At this site for Protocol MK-1654-007, 70 subjects were screened, 69 subjects were randomized, 67 subjects completed the study through Day 42 post Dose 1, and 66 subjects completed the full study (through Day 575). Of the two subjects who did not complete the study through Day 42 post Dose 1, subject (b) (6) in the clesrovimab group had consent withdrawn by their parent/guardian on Day 16, and subject (b) (6) in the clesrovimab group was terminated on Day 28 due to death from "reported abuse unrelated to the investigational products." Subject (b) (6) in clesrovimab group was lost to follow up.

The inspection evaluated the study records for 18 of the 69 randomized subjects for Protocol MK-1654-007. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; Independent Ethics Committee (IEC) submissions and approvals; subject eligibility criteria; source records, including medical records; primary safety

endpoint data of interest to the review division; adverse event reporting; protocol deviations; drug accountability logs; monitor logs and sponsor reports; and other regulatory documentation. Informed consent process and documents were reviewed for all subjects.

During the inspection, paper records were reviewed for the following adverse events, which comprised the primary safety endpoints of interest to the review division:

- Solicited injection-site AEs from Days 1 through 5 after each dose
- Solicited daily body temperature, with fever defined as rectal temperature ≥102.2°F (≥39.0°C) or axillary temperature ≥101.7°F (≥38.7°C) from Days 1 through 5 after each dose
- Anaphylaxis/hypersensitivity AESI from Days 1 through 42 post Dose 1
- Rash AESI from Days 1 through 42 post Dose 1

These items were verified against the data line listings provided by the sponsor for these 18 of the randomized subjects. No discrepancies were noted.

Other adverse events were reviewed for these 18 randomized subjects. The site failed to report increasing ringworm for subject (b) (6) (in the clesrovimab group). There was no other evidence of underreporting of adverse events.

Reviewer's comment: The single unreported adverse event (increasing ringworm in subject (b) (6) from the clesrovimab group) is not included in the proposed label. We recommend the review division consider this unreported AE.

4. **Maria Candela Etchegaray, MD**
   Site # 1001
   Protocol: MK-1654-004
   Hospital Militar Central Cir Mayor Cosme Argerich
   Avenida Luis María Campos 726, 8th Floor
   CABA, Buenos Aires C1426
   Argentina
   PDUFA Inspection Dates: March 25-31, 2025

At this site for Protocol MK-1654-004, 75 subjects were screened, 75 subjects were randomized, 75 subjects completed the study through the primary efficacy time frame (150 days), and 66 subjects completed the study at this site (Day 515). Of the 9 subjects that did not complete the full study, all were lost to follow up (subject (b) (6) in the placebo group, and subjects (b) (6) in the clesrovimab group) except for subject (b) (6) in the clesrovimab group, whose legal representative withdrew consent.

The inspection evaluated the study records for 15 of the 75 randomized subjects for Protocol MK-1654-004. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; Independent Ethics Committee (IEC) submissions and approvals; informed consent forms and process; subject eligibility criteria; informed consent process and forms; source records, including medical records; primary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; monitor logs and sponsor reports; and other regulatory documentation.

During the inspection, for these 15 randomized subjects who completed the study through Day 150, the primary efficacy endpoint data – clinical signs and symptoms (wheezing, chest wall in-drawing/retractions, rales/crackles, hypoxemia, tachypnea, or dehydration due to respiratory symptoms and cough/difficulty breathing) and NP sample RT-PCR results – were reviewed in paper/EMR format and PDF format, respectively. The clinical signs and symptoms data were verified against both the data line listings provided by the sponsor and those generated by this reviewer using the line listings generator, and the RT-PCR results were verified against the data line listings provided by the sponsor. The following two discrepancies were noted.

Source documents reviewed during the inspection showed that subject (b) (6) (placebo group) had RSV-positive RT-PCR test results (on Day 56) with cough and wheezing, therefore meeting criteria for RSV-associated MALRI. This case was reported in the data line listings.

Reviewer's comment: Because subject (b) (6) *was randomized to the placebo group, failure to report this case should favor placebo over clesrovimab. Therefore, this discrepancy should not have a meaningful effect on the determination of efficacy for this application.*

Adverse events were reviewed for these 15 randomized subjects. There was no evidence of underreporting of adverse events.

5. **Jose Manuel Novoa Pizarro, MD**
   Site # 1101
   Protocol: MK-1654-004
   Hospital Padre Hurtado
   Esperanza 2150
   San Ramon
   Santiago, Region M. de Santiago
   8880465
   Chile
   PDUFA Inspection Dates: April 7-11, 2025

At this site for Protocol MK-1654-004, 113 subjects were screened, 113 subjects were randomized, and 113 subjects completed the study through the primary efficacy time frame (150 days), and 112 subjects completed the study through Day 180. Data regarding subject disposition was not available for Days 181-515.

The inspection evaluated the study records for 50 of the 113 randomized subjects for Protocol MK-1654-004. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; Independent Ethics Committee (IEC) submissions and approvals; informed consent forms and process; subject eligibility criteria; source records, including medical records; primary efficacy endpoint data; adverse event reporting; protocol deviations; drug accountability logs; monitor logs and sponsor reports; and other regulatory documentation.

During the inspection, for these 50 randomized subjects who completed the study through Day 150, the primary efficacy endpoint data – clinical signs and symptoms (wheezing, chest wall in-drawing/retractions, rales/crackles, hypoxemia, tachypnea, or dehydration due to respiratory symptoms and cough/difficulty breathing) and NP sample RT-PCR results – were reviewed in paper format and PDF format, respectively. The clinical signs and symptoms data and the RT-PCR results were verified against the data line listings generated by this reviewer using the line listings generator. No discrepancies were noted.

Adverse events were reviewed for these 50 randomized subjects. The inspection found the following two adverse events were not reported: nasal mucus/sneezing (subject (b) (6), clesrovimab group), mild colic (subject (b) (6), clesrovimab group). Additionally, subject (b) (6) in the placebo group experienced irritability and defecation problem, but this was reported only as "irritability."

Reviewer's comment: The three unreported adverse events noted above – nasal mucus/sneezing, mild colic, and defecation problem – are referred to the review division. Given that "defecation problem" occurred in a subject taking placebo and the remaining AEs (in subjects in the clesrovimab group) appear mild in nature (nasal mucus/sneezing and mild colic), these unreported AEs are unlikely to meaningfully affect the safety analysis for this application.

6. **Merck Sharp & Dohme LLC**
   Protocol: MK-1654-004
   Protocol: MK-1654-007
   126 East Lincoln Ave.
   P.O. Box 2000
   Rahway, NJ 07065
   PDUFA Inspection Dates: March 13-27, 2025

This inspection covered the sponsor practices primarily related to MK-1654-004 and MK-1654-007. The inspection focused on the adequacy of the overall process for safety evaluation and reporting, including the selection of monitors, monitoring procedures and activities, quality assurance, safety/AE reporting, and data collection and handling, as well as records retention, financial disclosures, and electronic records.

The inspection reviewed the following activities and found them to be generally adequate:

- Clinical investigator selection and training
- Monitor qualifications, selection, and documentation of training
- Site monitoring procedures and activities
- Completion of monitoring reports and letters
- Data collection and handling
- Independent Data Monitoring Committee records
- Quality assurance audits
- Safety and adverse event reporting procedures
- Compliance with monitoring plans for safety oversight
- Medical monitor activities

- Procedures and access controls in instances of unblinding
- Electronic records and electronic signatures
- Custody and retention of records
- Maintenance of financial disclosure forms
- Maintenance of adequate records showing receipt and shipment of the investigational product (could not do a full reconciliation)
- Contracts with service providers, delegation of tasks within contracts, standard operating procedures specified in the contract, and meetings with service providers
- Selection of service providers, outsourced services, contractual agreements, and sponsor oversight of service providers
- Identification, selection, and management of service providers
- Clinicaltrials.gov components

{See appended electronic signature page}

Elena Boley, M.D., M.B.A.
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OSI/DCCE/GCPAB/Reviewer/Elena Boley
OSI/GCPAB/Program Analyst/Yolanda Patague

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ELENA BOLEY
05/05/2025 11:06:49 AM

PHILLIP D KRONSTEIN
05/05/2025 11:10:26 AM

JENN W SELLERS
05/05/2025 11:42:25 AM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – GLASS LUER PRE-FILLED SYRINGES

Date	3/19/2025
To:	Nailing Zhang
Requesting Center/Office	CDER/OND
From	Cassandra O'Donnell OPEQ/OHT3/DHT3C
Through (Team)	Rong Guo, Acting Team Lead, Injection Team OPEQ/OHT3/DHT3C
Through (Division) *Optional	Shruti Mistry, Assistant Director, Injection Team OPEQ/OHT3/DHT3C
Subject	ICCR: 01032423 ICC: 2401068 Submission: BLA761432 Sponsor: Merck Sharpe and Dohme LLC Drug/Biologic: MK-1654 Indications for Use: Prevention of respiratory syncytial virus lower respiratory tract disease in Neonates and infants who are born during or entering their first RSV season. (b) (4) [redacted].
Recommendation	**Filing Recommendation Date:** 12/06/2024 ☐ CDRH did not provide a Filing Recommendation ☐ Device Constituent Parts of the Combination Product are acceptable for Filing. ☑ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing **Final Recommendation:** ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with the following Post-Market Requirements/Commitments, ☐ Device Constituent Parts of the Combination Product are Not Approvable with the following CR Deficiencies **Comments to Review Team:** The Luer-lock components of the pre-filled syringe in BLA761432 are acceptable. After interactive review, the sponsor provided the required essential performance requirements for the Luer-lock per ISO 80369-7 by leveraging syringe manufacturer's data. **PMC/PMR or CR Deficiencies:** Not applicable

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
CASSANDRA K. O'DONNELL -S 2025.03.21 09:09:51 -07'00'	Rong Guo -S Digitally signed by Rong Guo -S Date: 2025.03.21 12:22:23 -04'00'	

1. PURPOSE

This review provides an assessment of the syringe device constituent part of the prefilled syringe product.

This review will cover the following review areas:

☒ Device constituent performance[1]

This review will not cover the following review areas:

☒CDRH Quality Systems Assessment / Facilities*
☒ Drug product/container closure performance
☒ Biocompatibility
☒ Sterility
☒ Human factors
☒ Control Strategy

*It was determined that a device quality systems / facilities assessment is not required for this product because the product is not an emergency (i.e., life-saving and essential[2]) treatment that are administered by non-health care professionals.

2. DEVICE DESCRIPTION

2.1. Picture of Final Device Presentation

Figure 1 Clesrovimab PFS consisting of Prefilled Syringe Assembled with Backstop and Plunger Rod.

[1] The scope of this review will be limited to the device constituent performance in accordance with FDA recognized versions of ISO 80369-7, ISO 594-1, ISO 594-2 and FDA guidance *Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices*. For a PFS with a luer connector, the review will be limited to luer connectivity performance requirements and will not cover functions of the primary container/simple syringe (dose accuracy/container content, breakloose force, glide force, cap removal) and their control strategy. There are no control strategy considerations for luer connectivity. Additional review may be warranted for any co-packaged devices, as applicable.

[2] Examples of emergency, life-saving and essential treatments include those used for conditions such as anaphylaxis or cardiac arrest and others in which failure of drug delivery may expose the patient to the reasonable likelihood of serious injury or death.

2.2. Design Requirements

Syringe Description

The syringe is a (b) (4) 1.5 mL Type 1 glass syringe with a Luer lock adapter and (b) (4) round flange.

Table 1 Clesrovimab PFS Component Descriptions

Component	Component Description	Compendial/ ISO Testing
Syringe Barrel Assembly	(b) (4) 1.5 mL syringe, Type I glass, with luer-lock adaptor; (b) (4) (b) (4)	USP<660> Ph. Eur. 3.2.1 ISO 11040-4 ISO 10993
	(b) (4) rigid tip cap (b) (4) (b) (4),	
Plunger Stopper	(b) (4) latex-free (b) (4) plunger stopper (b) (4)	ISO 8871-2 USP<381> Ph. Eur. 3.2.9 ISO 10993
Plunger Rod	(b) (4) plunger (b) (4)	ISO 10993
Backstop	(b) (4) backstop	ISO 10993
(b) (4)		

The sterilization method and sterilization site for the product contact components are outlined in **Table 2.**

Requirement	Describe
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Professional Use

Injection Site	Intramuscular/Upper Thigh
Injection tissue	Intramuscular

3. DEVICE PERFORMANCE REVIEW

Performance is located in

Manufacturer Reports

ISO 80369-7:2021 *Small-bore connectors for liquids and gases in healthcare applications-Part 7: Connectors for intravascular or hypodermic applications*					**Test Article: MK-1654, Clesrovimab Pre-filled Syringe (b) (4) 1.5 mL Type 1 glass syringe with a Luer Lock)**	
REQ	**Test Requirements**	**Sample Size**	**Stability**	**Transportation?**	**Verification Results**	**LR Comments**
6.1.3	**POSITIVE PRESSURE LEAKAGE** For a non-locking (slip) connector, assemble by applying an axial force of between 26.5 N and 27.5 N for 5 s to 6 s while rotating the connector under test to a torque of between 0.08 N·m and 0.10 N·m and a rotation not exceeding 90°. For a locking connector with fixed threads, assemble by applying an axial force of between 26.5 N and 27.5 N for 5 s to 6 s while rotating the connector under test to a torque of between 0.08 N·m and 0.12 N·m. Seal the assembly outlet and bring the internal water pressure to an effective pressure of 300kPa to 30kPa. Maintain the pressure for 30s ~ 35s. **Acceptance Criteria: There should be no leakage sufficient to form a falling drop of water.**	N=32	3-years Real Time Aging N=30	Yes Simulated Shipping Vibration Drop	Pass (no falling drops observed)	Sponsor leveraging (b) (4) Test Reports for Luer Lock Performance
6.2	**SUB-ATMOSPHERIC PRESSURE** For a non-locking (slip) connector, assemble by applying an axial force of between 26.5 N and 27.5 N for 5s to 6s while rotating the connector under test to a torque of between 0.08 N·m and 0.10 N·m and a rotation not exceeding 90°.For a locking connector with fixed	N=32	3-years Real Time Aging N=30	Yes Simulated Shipping Vibration Drop	Pass (no leak)	Sponsor leveraging (b) (4) Test Reports for Luer Lock Performance

	threads, assemble by applying an axial force of between 26.5 N and 27.5 N for 5s to 6s while rotating the connector under test to a torque of between 0.08 N·m and 0.12 N·m. Apply the sub-atmospheric pressure to an effective pressure of 80~88 kPa and close the valve. **Acceptance Criteria:** **The assembly shall not leak by more than** (b) (4) **Pa·m3 /s**					
6.3	**STRESS CRACKING W/LEAKAGE BY PRESSURE DECAY** For a non-locking (slip) connector, assemble by applying an axial force of between 26.5 N and 27.5 N for 5 s to 6 s while rotating the connector under test to a torque of between 0,08 N·m and 0,10 N·m and a rotation not exceeding 90°. For a locking connector with fixed threads, assemble by applying an axial force of between 26.5 N and 27.5 N for 5 s to 6 s while rotating the connector under test to a torque of between 0.08 N·m and 0.12 N·m. Seal the assembly outlet and bring the internal water pressure to an effective pressure of 300kPa to 330kPa Maintain the pressure for 30s ~ 35s. **Acceptance Criteria:** **There should be no leakage sufficient to form a falling drop of water.**	N=32	3-years Real Time Aging N=30	Yes Simulated Shipping Vibration Drop	Pass (no falling drop observed)	Sponsor leveraging (b) (4) Test Reports for Luer Lock Performance
6.4	**RESISTANCE TO SEPARATION FROM AXIAL LOAD** For non-locking (slip) connector, assemble by applying an axial force of between 26.5 N and 27.5 N for 5 s to 6 s while rotating the connector under test to a torque of between 0,08 N·m and 0,10 N·m and a rotation not exceeding 90°.	N=32	3-years Real Time Aging N=30	Yes Simulated Shipping Vibration Drop	Pass (no detachment from reference connector)	Sponsor leveraging (b) (4) Test Reports for Luer Lock Performance

	For a locking connector with fixed threads, assemble by applying an axial force of between 26.5 N and 27.5 N for 5 s to 6 s while rotating the connector under test to a torque of between 0.08 N·m and 0.12 N·m. Apply the axial force of 25N for luer slip connector and 35N for luer lock connector in a direction away from the test fixture at a rate of approximately 10 N/s until the minimum specified force is reached. Hold the axial force for 15s**.** **Acceptance Criteria:** **The connector should not completely detach at the interface between the connectors.**					
6.5	**RESISTANCE TO SEPARATION FROM UNSCREWING** For a non-locking (slip) connector, assemble by applying an axial force of between 26.5 N and 27.5 N for 5s to 6s while rotating the connector under test to a torque of between 0.08N·m and 0.12N·m. For a locking connector with fixed threads, assemble by applying an axial force of between 26.5 N and 27.5 N for 5 s to 6 s while rotating the connector under test to a torque of between 0.08 N·m and 0.12 N·m. Apply the unscrewing torque (0.019 8 N·m to 0.020 0 N·m) on the samples for 10s to 15s. **Acceptance Criteria:** **The connector should remain attached to the test fixture.**	N=32	3-years Real Time Aging N=30	Yes Simulated Shipping Vibration Drop	Pass (no detachment from reference connector)	Sponsor leveraging (b) (4) Test Reports for Luer Lock Performance
6.6	**RESISTANCE TO OVERRIDING** Assemble the components by applying an axial force of between 26.5 N and 27.5 N for 5 s to 6 s while rotating the connector under test to a torque of between 0.08 N·m and 0.12 N·m.	N=32	3-years Real Time Aging N=30	Yes Simulated Shipping Vibration Drop	Pass (no overriding of threads or lugs)	Sponsor leveraging (b) (4) Test Reports for Luer Lock Performance

	For a connector with a floating or rotatable collar, assemble by introducing the mating features (i.e., connector taper) together with and axial force of between 26.5 N and 27.5 N for 5s to 6s while rotating the collar of the connector under test to a torque of between 0.08 N·m and 0.12 N·m. Apply a torque (0,15 N·m to 0,17 N·m) and hold for 5 s 10 s. **Acceptance Criteria:** **The threads or lugs of the reference connector shall not completely extend past the threads or lugs of the connector and there shall be no cocking of the connectors.**					

Table 4: Syringe Barrel Supplier Luer Lock Adaptor Testing per ISO 80369-7

Test	Acceptance Criteria	Test Results		Overall Result	Test Report Reference
		T0 Result	T=3 yr RT*		
Positive pressure liquid leakage	Refer to **Attachment 2**	32/32 Pass	30/30 Pass	Pass	**Attachment 2**
Sub atmospheric pressure air leakage		32/32 Pass	30/30 Pass	Pass	
Stress cracking followed by leakage by pressure decay		32/32 Pass	30/30 Pass	Pass	
Resistance to separation from axial load		32/32 Pass	27/27 Pass	Pass	
Resistance to separation from unscrewing		32/32 Pass	30/30 Pass	Pass	
Resistance to Overriding		32/32 Pass	30/30 Pass	Pass	
Functional test with needle		32/32 Pass	N/A	Pass	

*Real Time (RT) aging was conducted at 30°C for 3 years.

Reviewer Comments

The device component of the combination product is a pre-filled glass syringe with Luer-lock. The sponsor, Merck Sharp & Dohme, LLC. provided a letter of authorization in **Module 1.4.2** to leverage (b) (4) 1.5mL Type I glass syringe: **DMF** (b) (4)

Upon initial review, the sponsor provided baseline and stability data for container closure integrity tests. However, the sponsor did not provide baseline, stability, or preconditioning data of the essential performance requirements (EPRs) associated with the Luer lock per ISO 80369-7 for the final finished combination product. IR#1 requested the sponsor provide the EPRs with statistical analysis and justified sample size per ISO 80369-7.

In response to IR#1, Merck supplied test reports on Luer-lock performance of the syringe from (b) (4) in **Module 1.11.1**. The sponsor stated that they are leveraging the syringe manufacturer's data for Luer-lock EPRs per ISO 80369-7. (b) (4) provided methodology, reports, validation criteria and for the following EPRs: positive pressure leakage, sub-atmospheric pressure, stress Cracking, resistance to separation from axial load, resistance to separation from unscrewing, and resistance to overriding. The syringes were tested and baseline and at shelf-life (b) (4) years, real-time aging). Sample size for all EPRs at baseline was n=32 and n=30 for stability. Merck also provided simulated shipping, drop, and vibration reports from (b) (4)

The data presented for the Luer-lock component of the pre-filled syringe within BLA761432 are acceptable.

Deficiencies were provided to the RPM on 02/06/2025.

Information Request #1	1. You provided a summary of your device essential performance requirement (EPR) testing methods and results in 3.2P.5.2 Analytical Procedures and 3.2.P.5.3 Validation of Analytical Procedures, respectively. You included tests for break loose force, extrusion force, and container closure integrity. However, you did not provide data on the EPRs of the luer lock adaptor of your syringe per ISO 80369-1: 2018 Small-bore connectors for liquids and gases in healthcare applications - Part 1: General requirements and ISO 80369-7:2021 Small-bore connectors for liquids and gases in healthcare application- Part 7: Connectors for intravascular or hypodermic applications (i.e. dimensional analysis, leak test, stress cracking, resistance to separation from axial load, resistance to separation from unscrewing, and resistance to overriding). This is not an exhaustive list and product specific factors should influence your EPR selection. This information is needed to ensure that the Luer lock feature of your device appropriately functions to prevent accidental needle sticks, leaking of the drug product, or patient injury due to premature needle separation from the device. a) Therefore, please provide test reports with data supporting your findings that include all the essential performance requirements specific to your device type. b) Please provide the chosen sample size for all EPRs with a statistical analysis of your data or an adequate statistical rationale for the chosen sample sizes are acceptable given the risks of device failure. While the chosen sample sizes should be based on your risk assessment, we recommend that the sample sizes for performance attributes that are associated with a high level of risk support a high level of statistical assurance that the device meets its specifications (e.g., 95% reliability with 99% confidence) since device failures may lead to serious adverse events including user injury and exposure to bloodborne pathogens. c) Please provide any documentation and data to support the Luer lock safety of your combination product to a sufficient reliability and up to its proposed shelf-life per ISO 80369-1: 2018 Small-bore connectors for liquids and gases in healthcare applications - Part 1: General requirements You may exclude certain essential performance results from the stability study if you can provide scientific rationale that the excluded EPR is unlikely to change over time. Malfunction of the Luer lock could lead to accidental needle sticks, leaks, or patient injury due to premature detachment of the needle. Therefore, ensure the provided testing is performed after pre-conditioning representative

	of intended use (e.g., shipping, drop) and to a reliability commensurate with the risk (e.g., 99% reliability) of the device.
Sponsor Response	Sponsor provided the syringe manufacturer's testing per ISO 80369-7 to leverage the Luer-lock performance requirements. The manufacturer's reports included a sample size of n=32 for baseline and n=30 for shelf-life. The sponsor also provided documentation of the manufacturer's simulated shipping report.
Reviewer Comments	The provided testing is in accordance with the recommendations in ISO 80369-7:2021, and the chosen sample size (n=32) is adequate to ensure 95%/95% confidence reliability. All results passed acceptance criteria.
Response Adequate:	☑ **Yes** ☐ **No, See IR #**

<<END OF REVIEW>>

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 13, 2025
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	BLA 761432
Product Name, Dosage Form, and Strength:	clesrovimab-xxxx [a] injection, 105 mg/0.7 mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant Name:	Merck Sharp & Dohme LLC (Merck)
FDA Received Date:	October 10, 2024
TTT ID #:	2024-11251
DMEPA 1 Safety Evaluator:	Melina Fanari, R.Ph
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP

[a] The non-proprietary name suffix for this product has not yet been determined; therefore, the placeholder established name-xxxx is used throughout this review to refer to the non-proprietary name and suffix for this product.

1 INTRODUCTION

As part of the approval process for clesrovimab-xxxx injection, the Division of Antivirals (DAV) requested that we review the proposed Prescribing Information (PI), Patient Package Insert (PPI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS CONSIDERED

This section lists the materials considered for our review of BLA 761432.

Table 1. Materials Considered for this Review	
Materials Considered	**Appendix Section**
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 CONCLUSION

We evaluated the proposed PI and PPI and determined that they are acceptable from a medication error perspective, however, the proposed container label and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error Merck Sharp & Dohme LLC (Merck) in Section 4.

4 RECOMMENDATIONS FOR MERCK SHARP & DOHME LLC (MERCK)

Table 1. Identified Issues and Recommendations for Merck Sharp & Dohme LLC (Merck) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Container Label and Carton Labeling			
1.	As currently presented, the format for the expiration date is not defined.	We are unable to assess the proposed expiration date format from a medication safety perspective.	To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-

Table 1. Identified Issues and Recommendations for Merck Sharp & Dohme LLC (Merck) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).*
2.	Net quantity statement requires revisions.	Minimize wrong syringe size selection errors.	Revise the net quantity statements to read as follows: One 105 mg/0.7 mL single-dose prefilled syringe Or Ten 105 mg/0.7 mL single-dose prefilled syringes
Container Label			
1.	The established name is not at least half the size of the proprietary name.	We refer you to 21 CFR 201.10(g)(2) which states that the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary	Revise the established name to be in accordance with 21 CFR 201.10(g)(2).

Table 1. Identified Issues and Recommendations for Merck Sharp & Dohme LLC (Merck) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
		name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.	
2.	Consider small label requirements	Increase prominence of critical information.	Ensure the proprietary name and nonproprietary name along with the product strength, route of administration are legible on the prefilled syringe label. Per 21 CFR 201.10(i), small labels are required to have the following minimum amount of information: proprietary name, established name, product strength, Identifying lot or control number, name of manufacturer, packer, or distributor, and expiration date. Therefore, to create additional white space, consider removing the storage statements.
3.	Net quantity statement is in green.	Competes in prominence with the proprietary name and proper name. lack prominence on the principal display panel. The proprietary	Decrease the prominence of the net quantity statement by removing (b) (4)

Table 1. Identified Issues and Recommendations for Merck Sharp & Dohme LLC (Merck) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
		name and established or proper name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the principal display panel (PDP). We recommend increasing the prominence of the proprietary name and established name. Consider the use of different font type or size, bolding, color, or other means to achieve increased prominence. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).	
Carton Labeling			
1.	The carton labeling does not contain instructions that this product must be administered by healthcare provider only.	Failure to include instructions on the carton labeling may result in patients or caregivers administering the product, which may lead to medication errors.	We recommend adding the statement "Must be administered by a healthcare provider" to the carton labeling. The statement will help alert patients, caregivers, and healthcare providers (particularly pharmacies who may dispense the product directly to the patient) that the patient should take the product to their healthcare provider for administration.

Table 1. Identified Issues and Recommendations for Merck Sharp & Dohme LLC (Merck) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
2.	Storage section is missing “Store in original container” as stated in prescribing information.	Consistency of storage information.	Add the following statement to the storage section: “Store in original container”
3.	The SN, expiration date and lot # are located on the principal display panel. Additionally, on the 1-syringe carton the GTIN/SN is in on the PDP and expiration date and lot # on the side panel.	Proper product identification.	The SN, expiration date and lot # on the principal display panel should be relocated to the side panel. Additionally, on the 1-syringe carton the lot # and expiration date should be in human readable format next to the 2D barcode and combined into one area on a side panel.

APPENDICES: MATERIALS CONSIDERED FOR THIS REVIEW

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 1 presents relevant product information for received on October 10, 2024 from Merck Sharp & Dohme LLC (Merck).

Table 1. Relevant Product Information for Resclesvio	
Initial Approval Date	NA
Nonproprietary Name	clesrovimab-xxxx
Indication	Indicated for the prevention of RSV lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season
Dosage Form	injection
Strength	105 mg/0.7 mL
Route of Administration	Intramuscular
Dose and Frequency	<u>Neonates and Infants: First RSV Season</u> The recommended dose is 105 mg administered as a single intramuscular (IM) injection. For neonates and infants born during the RSV season, administer TRADEMARK starting from birth. For infants born outside the RSV season, administer TRADEMARK once prior to the start of their first RSV season considering (b) (4) duration of protection by TRADEMARK. *[See Clinical Pharmacology (12.2).]* <u>Infants Undergoing Cardiac Surgery with Cardiopulmonary Bypass</u> For infants undergoing cardiac surgery with cardiopulmonary bypass during the RSV season, an additional 105 mg dose is recommended as soon as the infant is stable after surgery to ensure adequate clesrovimab-xxxx serum levels.

<table>
<tr><th colspan="2">Table 1. Relevant Product Information for Resclesvio</th></tr>
<tr><td>How Supplied</td><td>Sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution supplied as follows:

Carton containing one or ten single-dose prefilled type I glass syringe(s) with Luer Lock and plunger stopper. The prefilled syringe is not made with natural rubber latex.
<table>
<tr><td>Prefilled syringe</td><td>Pack Size</td><td>NDC</td></tr>
<tr><td>105 mg/0.7 mL single-dose</td><td>Carton of 1</td><td>0006-5073-01</td></tr>
<tr><td>105 mg/0.7 mL single-dose</td><td>Carton of 10</td><td>0006-5073-02</td></tr>
</table>
</td></tr>
<tr><td>Storage</td><td>• Store prefilled syringes under refrigeration at 36°F to 46°F (2°C to 8°C).
• Keep the prefilled syringe in the original carton to protect from light until time of use.
• TRADEMARK may be kept at room temperature between 68°F to 77°F (20°C to 25°C) for a maximum of 48 hours. After removal from the refrigerator, TRADEMARK must be used within 48 hours or discarded.
• Do not freeze. Do not shake.</td></tr>
</table>

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following labels and labeling submitted by Merck Sharp & Dohme LLC (Merck).

- Prescribing Information and Patient Package Insert received on October 10, 2024, available from \\CDSESUB1\evsprod\BLA761432\0002\m1\us
- Container label and Carton labeling received on October 10, 2024

B.2 Container Label and Carton Labeling Images

(b) (4)

1 Page of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MELINA N FANARI
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YEVGENIYA M KOGAN
02/13/2025 02:03:01 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Consult Number:	ICCR #01032439
Document Number:	BLA 761432 MK-1654
Applicant:	Merck Sharp & Dohme LLC
Trade Name:	Clesrovimab injection
Consult Type:	In-vitro/Companion Diagnostic Devices
Requestor:	Michael Thomson
Requestor Home:	CDER
Gatekeeper / Consultant:	Daisy Torres-Miranda daisy.torres-miranda@fda.hhs.gov
Consultant Home:	CDRH\DMD\BAC2b
Date Requested:	November 19, 2024
Due Date:	December 23, 2024

I. Background

On November 19, 2024, case ICCR #01032439 was created regarding Biologics License Application (BLA 761432) by Merck Sharp & Dohme LLC (sponsor) for the evaluation of clesrovimab, also known as MK-1654. The FDA Center for Drug Evaluation and Research (CDER) has consulted the Center for Devices and Radiological Health (CDRH) Division of Microbiology Devices (DMD) to assist answering questions related to the sponsor's interference studies. Clesrovimab was granted US Fast Track Designation on August 27, 2018 by U.S. Food and Drug Administration (FDA). The clesrovimab clinical program supporting the marketing application includes: 3 Phase 1 studies – MK-1654-001 and MK-1654-003 in healthy adults only; MK-1654-008 in healthy adults, children, and infants. 1 Phase 1b/2a study – MK-1654-002 in healthy preterm and full-term infants. 1 Phase 2b/3 study – MK-1654-004 in healthy preterm and full-term infants, and 1 Phase 3 study – MK-1654-007 in infants and children at increased risk for severe Respiratory Syncytial Virus (RSV) disease. Clesrovimab has the potential to become the first and only approved immunization designed to protect infants with a single dose regardless of weight for the duration of their first RSV season. The sponsor includes a description of four interference studies, a summary of results and the sponsor's conclusions. This memorandum serves to answer CDER's questions and to comment on the applicant's assessment of interference of clesrovimab with rapid antigen detection testing (RADT) for RSV detection.

II. Product description (Intended Use):

Clesrovimab is an investigational extended half-life monoclonal fully human IgG antibody that binds with high affinity only to the RSV F protein, antigenic site IV. It is developed as a passive immunization for prevention of RSV lower respiratory tract disease (LRTD) in neonates and infants who are born during or entering their first RSV season (b) (4) The parental monoclonal antibody (mAb) of clesrovimab, clone RB-1, was isolated from human memory B-cells. Three (3) substitutions (YTE, M252Y/S254T/T256E) were introduced into the Fc region of RB-1 (RB-1-YTE) to generate clesrovimab. The YTE substitutions extend the half-life of clesrovimab by reducing clearance, thereby allowing it to protect infants an entire RSV season with a single dose administration, regardless of body weight and for the full duration of the RSV season.

III. Current therapies for RSV prevention and CDC recommendations:

Synagis (palivizumab; MedImmune, acquired by AstraZeneca) is a humanized mouse prophylactic mAb (IgG) produced by recombinant DNA technology, that targets the antigenic site II of the RSV F protein to prevent entry of the virus into cells. It was approved by the FDA in June 1998 and it is indicated for the prevention of serious LRTD caused by RSV in pediatric patients at high risk of RSV disease. Palivizumab is administered intramuscularly on a monthly basis during the infant's first RSV season (up to five doses at a dose of 15 mg/kg).[1,2] Although palivizumab is not widely prescribed due to high cost and the need for

[1] Label - Palivizumab (Synagis) Medimmune

[2] Palivizumab for preventing severe respiratory syncytial virus (RSV) infection in children - PMC

monthly IM dosing during the average 5-month RSV season in temperate climates due to its half-life, immunoprophylaxis with palivizumab has remained an option for children at high risk, as outlined in the 2014 American Academy of Pediatrics (AAP) policy statement.[3]

Beyfortus (nirsevimab; AstraZeneca) is a human mAb (IgG), that targets the antigenic site Ø on the RSV F protein. Beyfortus received approval by the FDA in July 2023 for the prevention of RSV LRTD in neonates and infants born during or entering their first RSV season, and children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.[4] In clinical studies, nirsevimab showed greater potency at inhibiting RSV than palivizumab in cell-culture and animal models and has an Fc region engineered to have an extended half-life in vivo.[5] On August 3, 2023, the Centers for Disease Control and Prevention (CDC's) Advisory Committee on Immunization Practices (ACIP) recommended nirsevimab for all infants aged <8 months who are born during or entering their first RSV season and for infants and children aged 8–19 months who are at increased risk for severe RSV disease and are entering their second RSV season.[6]

Three RSV vaccines are approved by the FDA for use in the United States:

- Arexvy (GSK), approved in May 2023, for individuals 60 years of age and older, and individuals 50 through 59 who are at increased risk for LRTD caused by RSV. [7]
- Abrysvo (Pfizer), approved in May 2023, for pregnant individuals at 32 through 36 weeks gestational age and in infants from birth through 6 months of age. Also, for individuals 60 years of age and older, and individuals 18 through 59 years of age who are at increased risk for LRTD caused by RSV.[8]
- mResvia (Moderna), approved in June 2024, for individuals 60 years of age and older.[9]

At the time of writing this memo, the CDC recommends RSV vaccination for all adults ages 75 and older and for adults ages 60–74 who are at increased risk of severe RSV (Arexvy, Abrysvo, or mRESVIA).[10] To protect infants from severe RSV, CDC recommends an RSV vaccine for pregnant people (Abrysvo), administered between weeks 32 to 36 of gestation or the monoclonal antibody (nirsevimab) given to the baby. [11]

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[3] Palivizumab Prophylaxis in Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection | Pediatrics | American Academy of Pediatrics

[4] Label- Beyfortus (nirsevimab) AstraZeneca

[5] Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants | New England Journal of Medicine

[6] Use of Nirsevimab for the Prevention of Respiratory Syncytial Virus Disease Among Infants and Young Children: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023

[7] Package Insert - AREXVY

[8] Package Insert - ABRYSVO

[9] Package Insert - mRESVIA

[10] RSV Vaccine Guidance for Older Adults | RSV | CDC

[11] RSV Vaccine Guidance for Pregnant People | RSV | CDC

IV. CDER Questions directed to CDRH:

Regarding the original BLA 761432 (clesrovimab) submission, CDER requested CDRH input on the applicant's assessment of interference by clesrovimab with RADT for RSV detection, other studies that they may need to conduct, and product labeling. Specifically, CDER provided 5 questions:

1. Which other commonly used RSV rapid antigen tests should be assessed for interference by clesrovimab?

The document "Virology report: MK-1654 Global RSV surveillance and clinical virology report" page 30, section 4: "Impact of clesrovimab on RSV antigen based diagnostic assays" describes four RSV rapid antigen tests kits that were evaluated for detection of RSV A in the presence or absence of clesrovimab. These include the BinaxNOW RSV (Abbott), TRU RSV (Meridian), Remel Xpect RSV, and the BD Veritor System. The sponsor stated in page 31: "The positive controls from each RSV kit were spiked with clesrovimab to final concentrations of 1 and 5 µg/mL, the higher concentration having been selected based on nasal concentrations determined in Phase 1 adult studies and expected pharmacokinetics at the 105 mg dose in infants. The clesrovimab spiked samples were tested according to the respective manufacturer's protocol. Positive controls from the different kit manufacturers have unknown titers of virus equivalent. Therefore, additional samples of RSV-A (ATCC cat. # VR-1540) with defined viral titers (covering a range of 10^6 to 10^2 PFU/mL) were included in the testing to overcome the inherent variability of the kits' positive controls. This step facilitated studying the interference of clesrovimab with the kit reagents independent of the variable titers of positive controls provided by the manufacturers."

After review of the interference studies (with defined viral titers, not individual positive controls), the following results were noted by the sponsor:

- **BinaxNOW RSV kit (Abbott)**: clesrovimab interference was observed at viral titers ≥10^4 PFU/mL (with 1 and 5 µg/mL of clesrovimab). In the absence of clesrovimab (0 µg/mL), the BinaxNOW RSV test detected RSV A down to titers of 10^4 PFU/mL. Also, in the presence of clesrovimab there was a qualitative impact on the readout (band intensity) of this test.

BinaxNOW	Virus Titer (PFU/mL)					No virus
Clesrovimab (µg/mL)	10^6	10^5	10^4	10^3	10^2	
5	Pos	Pos	Neg	Neg	Neg	Neg
1	Pos	Pos	Neg	Neg	Neg	Neg
0	Pos	Pos	Pos	Neg	Neg	Neg

Pos=Positive; Neg=Negative; PFU=plaque forming units; RSV=respiratory syncytial virus.

- **Remel Xpect RSV kit**: clesrovimab interference was observed at viral titers ≥10^5 PFU/mL (at 5 µg/mL of clesrovimab). In the absence of clesrovimab, the Remel Xpect RSV test detected RSV A down to titers of 10^5 PFU/mL.

Remel Xpect RSV	Virus titer (PFU/mL)				No virus
Clesrovimab (µg/mL)	10^6	10^5	10^4	10^3	
5	Pos	Neg	Neg	Neg	Neg
1	Pos	Pos	Neg	Neg	Neg
0	Pos	Pos	Neg	Neg	Neg

Pos=Positive; Neg=Negative; PFU=plaque forming units; RSV=respiratory syncytial virus

- **TRY RSV kit (Meridian)**: No interference by clesrovimab with RSV detection was noted at viral titers ≥10^5 PFU/mL . In the absence of clesrovimab, the TRU RSV kit detected RSV A down to titers of 10^5 PFU/mL. Also, in the presence of clesrovimab there was a qualitative impact on the readout of this test.

RSV TRU	Virus Titer (PFU/mL)					No Virus
Clesrovimab (µg/mL)	10^6	10^5	10^4	10^3	10^2	
5	Pos	Pos	Neg	Neg	Neg	Neg
1	Pos	Pos	Neg	Neg	Neg	Neg
0	Pos	Pos	Neg	Neg	Neg	Neg

Pos=Positive; Neg=Negative; PFU=plaque forming units; RSV=respiratory syncytial virus.

- **BD Veritor**: No interference by clesrovimab with RSV detection was noted at viral titers ≥104 PFU/mL for RSV BD Veritor RSV kit. The absence of clesrovimab (0 µg/mL), the BD Veritor test detected RSV A down to titers of 10^4 PFU/mL.

BD Veritor	Virus titer (PFU/mL)				No virus
Clesrovimab (µg/mL)	10^6	10^5	10^4	10^3	
5	Pos	Pos	Pos	Neg	Neg
1	Pos	Pos	Pos	Neg	Neg
0	Pos	Pos	Pos	Neg	Neg

Pos=Positive; Neg=Negative; PFU=plaque forming units; RSV=respiratory syncytial virus

CDRH reviewer comments:

To evaluate for mAb interference, Merck Sharp & Dohme LLC described using similar RADT to those previously used by AstraZeneca and MedImmune in the presence or absence of nirsevimab or palivizumab (with 10^5 PFU/mL RSV A or B, mAb at final concentrations of 1 and 10 µg/mL), respectively, as part of their analytical studies for product validation. These tests were considered as the most commonly used according to the College of American Pathologists at that time, which included: the BinaxNOW RSV

(Abbott, K032166), the TRU RSV (Meridian Bioscience, K071101), the Remel Xpect RSV (Remel, K022845), the BD Directigen EZ RSV test kit (BECTON DICKINSON & CO, K022133), and the Quidel QuickVue RSV test kit (Quidel, K070747).
Merck Sharp & Dohme LLC (clesrosvimab) study report states that the BD Directigen EZ RSV kit has been discontinued by the manufacturer and could not be procured for testing, instead the BD Veritor System (BD, K121633) was used. The QuickVue RSV test kit was evaluated with nirsevimab and palivizumab but not with clesrovimab. After palivizumab was cleared in the US in 1998, further interference studies have show interaction with additional RADT.[12]
The results provided by the sponsor shows that clesrovimab could compete with antibodies that bind the same or overlapping epitopes, including those that are critical components of some RSV diagnostic assays.[13] Clesrovimab interference with these immunoassays might lead to false-negative results and contribute to inappropriate use of antibiotics and unnecessary laboratory testing, prolonged hospitalizations and delay actions to limit nosocomial infections. [6,7,14,15]
Although further premarket clinical testing can be feasible, this reviewer agrees with the sponsor's conclusion from the data, that "for rapid antigen diagnostic kit results, which are negative when clinical observations are consistent with RSV infection, it is recommended to confirm using an RT-PCR-based assay", if confirmed that there is no interference when studies done. Demonstration of interference with forementioned commonly used assays (Binax NOW RSV and Remel Xpect RSV kits) are probably enough to consider appropriate safety mitigations as limitations and labeling provisions where individuals who have received clesrovimab prophylaxis to consider that a negative result does not preclude RSV infection, these tests should be interpreted with caution and that all negative test results should be confirmed by cell culture or nucleic acid amplification tests (NAATs), such as real-time reverse transcription-polymerase chain reaction (RT-PCR).[12] NAATs cleared under regulations 21 CFR 866.3980 and 866.3981 may be better alternatives to RSV Ag tests if no interference from this is observed with preventative RSV mAb.

This reviewer does not recommend a particular RADT over the others for further interference studies. In vitro antigen diagnostic RSV devices intended to detect and identify RSV from human respiratory specimens are regulated under 21 CFR 866.3480, Respiratory syncytial virus serological reagents, which include lateral flow rapid antigen tests, chromatographic/enzyme immunoassays (CIA/EIA) under product code GQG. It may also be relevant for the sponsor to consider conducting interference studies with

[12] Potential for Palivizumab Interference With Commercially Available Antibody–antigen Based Respiratory Syncytial Virus Diagnostic Assays - The Pediatric Infectious Disease Journal
[13] Developments in immunologic assays for respiratory viruses - PubMed
[14] The effect of rapid respiratory viral diagnostic testing on antibiotic use in a children's hospital - PubMed
[15] Rapid testing for respiratory syncytial virus in a paediatric emergency department: benefits for infection control and bed management - PubMed

commonly used direct or indirect immunofluorescence assays (DFA/IFA), under product code LKT.

2. Which antigenic sites are targeted by each rapid antigen test, and is the interference specific for assays that target Site IV (clesrovimab target)?

CDRH reviewer comments: Lateral flow immunoassay kits do not disclose the specific antigenic target site(s) of their antibody composition. Currently authorized RSV antigen tests do not describe the antibodies used in the manufacture of an antigen test in their labeling, reactivity to specific mAb has not been tested in many of these tests, nor antibody names appear in the intended use statements of RSV devices. To the best of this reviewer's knowledge, only wet testing like the ones described in the "Impact of clesrovimab on RSV antigen based diagnostic assays" could more definitively determine whether various levels of interference from clesrovimab can be present. For example, while interference has been observed with the BinaxNOW RSV assay and clesrovimab (with 1 and 5 µg/mL, at viral titers $\geq 10^4$ PFU/mL) that targets site IV, interference has also been reported with palivizumab that targets site II, in particular studies. Furthermore, interference can be affected by viral titer load and/or mAb concentrations. In the case of nirsevimab, antigenic site Ø–specific antibodies are distinct from neutralizing antibodies to other known antigenic sites on RSV F because of their exclusive recognition of the prefusion F structure and extremely high potency. Nonetheless, electron microscopy has showed that two other antibodies (e.g., AM22 and 5C4) can bound to antigenic site Ø. [16] CDRH cannot exclude that any particular monoclonal antibody is commercially available and/or eventually used for the development of future antigen tests.

3. Are there other assessments that should be conducted by the Applicant (e.g., assessing with RSV subtype B)?

CDRH reviewer comments: While it is important to implement measures effective at preventing disease due to both RSV A and RSV B to ensure impactful public health interventions and prevention strategies that ensure both subgroups are targeted to avoid one subgroup becoming dominant and/or scaping immunity once prophylactic programs are deployed, RSV A and RSV B, both contribute substantially to the global RSV burden. Both RSV subgroups can cause significant disease and none of the available evidence to date suggests any differences in clinical severity between the subgroups. Rapid antigen tests that qualitatively detect RSV antigens regulated under 21 CFR 866.348 or potentially under the new regulation 866.3987 for multi-analyte respiratory virus antigen detection (at the time of writing this memo, RSV assays have not been validated under this regulation yet) are validated to identify either subtype and do not

[16] Structure of RSV Fusion Glycoprotein Trimer Bound to a Prefusion-Specific Neutralizing Ab | Science

necessarily differentiate between RSV A or B. [17,18] Very occasionally, monoclonal antibodies are found that appear to be subgroup-specific or subgroup-preferring. Data suggests that RSV F is relatively well conserved and highly similar between RSV A and B, although changes in the amino acid sequence have been observed.[19] The sponsor describes in the document "Virology report: MK-1654 Global RSV surveillance and clinical virology report", page 11, an evaluation of RSV F gene sequences in RSV-positive clinical samples. Based on the analysis of the F protein sequence from 555 RSV-positive samples (including A and B subtypes), the clesrovimab binding epitope on Site IV of the RSV F protein was highly conserved. From the clinical standpoint, this medical officer does not find further value in assessing RSV B subtype in additional interference studies. As mentioned above, the sponsor may consider conducting wet interference testing using DFA/IFA tests.

4. Are there rapid antigen tests targeting other RSV proteins which could be used as an alternative?

CDRH reviewer comments: Lateral-flow immunoassays for the detection of RSV typically target fusion (F) protein and/or a nucleoprotein (N) in human nasal wash, nasopharyngeal aspirate, or nasal/nasopharyngeal swab samples. The sponsor described using lateral flow tests, for their interference studies, that can identify one or both proteins (e.g., TRU RSV kit). Other examples of lateral flow tests that describe targeting the F protein, and/or the nucleoprotein antigen from RSV includes the NanoCheck RSV (Nano-Ditech, K240280) and the Sofia RSV FIA test (Quidel, K130398). The application of technology provides for the development of monoclonal antibodies to recognize other proteins (e.g., M, P, G), but may not detect all antigenic variants or new strains of RSV.[20] For a full updated list of antigen tests cleared for detection of RSV, and what technology each test use, you can review the decision summaries accessible through FDA access data RSV tests, using product code GQG and LKT.

5. How should the interference be reported in the clesrovimab label?

CDRH reviewer comments: In considering uncertainty in benefit-risk determinations, CDRH considers several factors including but not limited to the extent of probable benefits and risks of the device, the extent of uncertainty regarding the benefit-risk profile of approved or cleared alternative diagnostics, the extent of public health need, the feasibility of generating premarket clinical evidence, the ability to reduce or resolve the remaining uncertainty of the device's benefit-risk profile postmarket, and the likely

[17] Multi-analyte respiratory virus antigen detection
[18] Diagnostic Testing for RSV | RSV | CDC
[19] Differences Between RSV A and RSV B Subgroups and Implications for Pharmaceutical Preventive Measures - PMC
[20] Respiratory Syncytial Virus Genetic and Antigenic Diversity - PMC

effectiveness of mitigations such as labeling. [21] While remaining uncertainty of interference with commercially available RSV diagnostic tests can be addressed through a postmarket study, CDRH believes it is necessary to consider risk mitigation strategies to lower the probability of a harmful event occurring and improve the benefit-risk profile of the candidate product. Since RSV rapid antigen diagnostic tests do not preclude RSV infection, these kits carry disclaimers in labeling (including IFU and limitations) to advise these tests are not to be used as the sole basis for treatment or other management decisions. [22] It is recommended that negative test results be confirmed by viral cell culture or an alternative method, such as an FDA-cleared molecular assessment. Recently cleared assays also includes a limitation statement reporting that therapeutic anti-RSV monoclonal antibodies may interfere with the RSV test; monoclonal antibodies may fail to detect, or detect with less sensitivity, RSV viruses that have undergone minor amino acid changes in the target epitope region, (e.g., Nanocheck RSV kit). CDRH recognizes the potential for clesrovimab to interfere with diagnostic assays should be a consideration for the diagnostician and recommends that the interference of RSV diagnostic assays by clesrovimab to be disclosed in labeling to use caution when interpreting negative immunological assay results when clinical observations are consistent with RSV infection. A RT-PCR assay, if is not inhibited by clesrovimab, may prove useful for laboratory confirmation of RSV infection.

Daisy M. Torres Miranda -S

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[21] Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions - Guidance for Industry and Food and Drug Administration Staff

[22] Underascertainment of Respiratory Syncytial Virus Infection in Adults Due to Diagnostic Testing Limitations: A Systematic Literature Review and Meta-analysis - PMC

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